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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,520	BISHOP ET AL.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2007*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6,7,11,12,14-20,22-25,28,31-40,42-51 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6,7,11,12,14-20,22-25,28,31-40,42-51 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 18-19, 32, 40, 42-43, 45-46 and 51 have been amended, claims 1, 5, 8-10, 13, 21, 26-27, 29-30, 41 and 52 are cancelled and claim 53 has been added. Claims 2-4, 6-7, 11-12, 14-20, 22-25, 28, 31-40, 42-51 and 53 are under examination. It is noted that in the previous Office action mailed 4/10/2007, claims 19 and 42 were indicated as allowable if rewritten in independent form. However, after further consideration, new grounds of rejection have been applied below.

Claim Rejections - 35 USC § 112

Claim 43 has been amended to remove the phrase "weak promoter". Claims 45-46 has been amended to change dependency from claim 43 to claim 44. Therefore the rejection of claims 43-50 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's amendment to claim 43 and arguments, see REMARKS, filed 10/4/2007, with respect to the rejection(s) of claim(s) 43-48 and 50 under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record) in view of Sedivy et

al (of record) have been fully considered and are persuasive. Neither Capecchi et al or Sedivy et al teach a promoter that is a RSV promoter or a PGK promoter. Therefore, the rejection of claims 43-48 and 50 have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of additional prior art (see below).

Applicant's amendments and arguments, see REMARKS, filed 10/4/2007, with respect to the rejection(s) of claim(s) 49 under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record) in view of Sedivy et al (of record) in view of Pfarr (of record) have been fully considered and are persuasive. Neither Capecchi et al, Sedivy et al or Pfarr teach a promoter that is a RSV promoter or a PGK promoter. Therefore, the rejection of claim 49 has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of additional prior art (see below).

Claims 43-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record) in view of Sedivy et al (of record) and further in view of Czernilofsky et al (U.S. Patent No. 5,922,549, 7/13/1999). This is a NEW rejection necessitated by amendment to claim 43.

It is noted that claim 43 has been amended to further limit the promoter for the negative selection marker from a weak promoter or a PGK promoter, to a promoter that is a Rous Sarcoma Virus (RSV) promoter or a PGK promoter.

The teaching of Capecchi et al and Sedivy et al and the combination of the two to render obvious the targeting vector have been detailed in the previous Office action

(4/10/2007, pages 5-8, for example). The response to arguments submitted by the Applicants regarding Capecchi et al in view of Sedivy et al will be presented below. Capecchi et al teach a table showing contemplated regulatory sequences (i.e. promoters) for the positive and/or negative selection markers (see column 14, Table IIB, in particular). Capecchi et al or Sedivy et al do not specifically teach a vector with RSV promoter or PGK promoter.

Czernilofsky et al teach a cell comprising a plasmid which can be transfected into mammalian cells and integrated into the host genome, to enable expression of a reporter gene to take place under the control of regulatory elements (see column 7, lines 55-65, for example). Czernilofsky et al teach that the vector contains a dominant selection marker and that the choice of any specific selection marker is not critical. Czernilofsky et al teach that the RSV long terminal repeat (LTR) promoter is an example of a promoter that can drive the selection marker genes. Czernilofsky et al teach that the plasmids are preferably designed so that individual important elements such as the reporter gene, the promoter for the reporter gene and the regulatory sequences for the selection marker can easily be replaced or changed, in order to adapt to any modified requirements resulting from the special application (see column 8, lines 1-25, for example). Therefore, Czernilofsky et al meets the limitation of an RSV promoter for a selection marker on a plasmid vector.

It would be obvious to modify the targeting vector rendered obvious by Capecchi et al in view of Sedivy et al, and use an RSV promoter as taught by Czernilofsky et al in place of the promoters contemplated by Capecchi et al in Table IIB because the claimed

promoters were well known in the prior art and the substitution of one known element (i.e. RSV promoter) for another (e.g. CMV promoter) would yield predictable results to the skilled artisan at the time the invention was made. There is a reasonable expectation of success to use RSV promoter in place of a CMV promoter (for example) to regulate expression of a negative selection marker because these promoters are known in the art and Czernilofsky et al teach that the RSV promoter can drive expression of a selectable marker. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Capecchi et al (of record) in view of Sedivy et al (of record) and further in view of Czernilofsky et al render obvious somatic gene targeting vector comprising an RSV promoter operably linked to a negative selection marker **(claim 43)**.

Sedivy et al does contemplate use of the cre/lox system for recombination to introduce a positive selection marker into a genome. One of ordinary skill in the art would know that the term Lox refers to the recombination recognition sequence and the term Cre refers to Cre recombinase (**claim 44-46**).

Capecchi et al teach that SV-40 early can be used as a regulatory sequence, (see Table IIB), which meets the limitation of a vector with an SV40 polyadenylation sequence (**claim 48**).

Capecchi et al teach that the positive selection markers sequences can be neomycin (Neo) and that the negative selection marker can be diphtheria toxin (see

column 7, lines 18-20, Table I, in particular), which meets the limitation of **claims 47 and 50.**

Arguments/Response to Arguments

Applicants submit that the Examiner has not presented a proper analysis for patentability under 35 U.S.C. 103(a). Applicants submit that Capecchi et al do not disclose polyadenylation sequences operably linked to the positive selection marker, as recited by claim 43. Further, Applicants submit that Capecchi et al do not disclose excision of the positive selection sequences using site-specific recombination sequences, such as loxP sequences (as recited by claims 44-46). Instead, Capecchi et al teach that the positive selection sequences can be excised by homologous recombination (col. 11, lines 3-6). Applicants submit that Capecchi et al teach a detailed method where the positive selection marker is located in the intron of the targeted gene, and contains an independent functional promoter, i.e., it is not promoterless (col. 13, lines 27-56). Moreover, Applicants submit that Capecchi et al do not teach or suggest either the RSV promoter or the PGK promoter.

Applicants submit that Sedivy does not remedy the deficiencies of Capecchi et al. Sedivy discuss PNS vectors where the positively and negatively selectable genes are functionally independent expression cassettes, and each contains its own promoter and polyadenylation signals (p. 88, second column and Fig. 1). Applicants submit that Sedivy does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector. Applicants submit that

Sedivy mentions theoretically the possibility of sequential targeting of second allele, but provides no technical details in this review. Applicants submit that Sedivy cites a reference in which a cre/lox system was used in ES cells to recycle a targeting vector. In that paper, the cre/lox system is used to remove a PNS cassette (positive-negative selection cassette that includes both a promoter-driven neo resistance gene as well as a thymidine kinase gene). Applicants submit that this might allow the PNS cassette to be used in subsequent rounds of targeting. In contrast, Applicants submit that the present invention uses the site-specific recombination sequences to remove a promoterless neo gene (the promoterless neo gene is not considered a PNS cassette). Since Sedivy does not teach or suggest a promoterless positive selection marker, Sedivy can not teach the combination of a promoterless positive selection marker in combination with a cre/lox system. Applicants submit that since neither of the cited references teach nor suggest a promoterless PNS vector containing a polyadenylation sequence, the cited references even when combined do not teach or suggest all the features of claims 43-48 and 50. Further, Applicants submit that since neither reference teaches or suggests the use of site-specific recombination sequences in a promoterless PNS vector, and since neither reference teach or suggest the use of a PGK or RSV promoter, claims 43-48 and 50 are not obvious over the cited art.

Applicant's arguments filed 10/4/2007 have been fully considered but they are not persuasive. The Examiner disagrees with Applicants' submission that the rejection is rendered obvious by picking and choosing from the cited references to the exclusion of other parts. Each of the elements of the claimed gene targeting vector is

known in the art and portions are contemplated by each of the authors. It is not "exclusion of parts necessary to the full appreciation what the documents fairly suggest" to incorporate specific embodiments taught in the references into the rejection. The claimed vector could be envisaged in the cited references by the skilled artisan.

Applicants submit that Capecchi et al teach a detailed method where the positive selection marker is located in the intron of the targeted gene, and contains an independent functional promoter, i.e., it is not promoterless. However, the teaching is only one embodiment taught by Capecchi to be used in an instance such as gene therapy applications where disruption of the endogenous gene is undesirable (see col. 13, lines 27-56). Capecchi et al also teach embodiments in which the positive selection marker is promoterless until recombination with a target sequence places it under the control of the regulatory sequence in the target DNA sequence (see column 8, lines 27-35 and column 13, lines 7-20, in particular). Column 9, lines 10-16 teach a "promoterless positive selection marker" used as a third DNA sequence so that its expression is to be placed under the control of an endogenous regulatory region (i.e. of the target sequence).

Applicants submit that Sedivy et al does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector (p. 88, second column and Fig. 1). To the contrary, Sedivy et al do contemplate targeted homologous gene recombination in somatic cells using PNS vectors and using promoterless vectors (see page 88, left column, paragraph 2, bridging to right column, and Figure 1 for example). However, it is not necessary for Sedivy et al

to teach a promoterless selection marker, since this limitation is met by Capecchi et al. Similarly, it is not necessary for Sedivy et al to specifically teach the combination of a promoterless positive selection marker in combination with a cre/lox system. It is the combination of Capecchi et al and Sedivy et al that renders this combination obvious. Whether or not the positive selection marker has a promoter does not impact the reasonable expectation of success in being able to use a cre/lox recombination system as taught by Sedivy with the vector comprising a promoterless positive selection marker.

Capecchi et al teach that the positive selection marker can in some cases comprise a polyadenylation sequence (see column 13, lines 26-49, in particular) It is true that Capecchi et al do not disclose excision of the positive selection sequences using site-specific recombination sequences, such as loxP sequences (as recited by claims 44-46). Capecchi et al do teach that the positive selection sequences can be excised by homologous recombination. In addition, Sedivy do discuss PNS vectors where the positively and negatively selectable genes are functionally independent expression cassettes, and each contains its own promoter and polyadenylation signals (p. 88, second column and Fig. 1). However, it is the combination of these two references that renders obvious the claimed method.

As disclosed in the previous Office action, it would have been obvious to the skilled artisan at the time of the invention to modify the teaching of Capecchi et al to include polyadenylation sequences and cre/lox recombinase recognition sites in the PNS vector because Capecchi et al teach that to modify gene expression, different

regulatory sequences can be used and combined (column 13, lines 65-67, in particular) and Sedivy et al teaches that polyadenylation sequences flank the positive and negative selection sequences in PNS vectors. Polyadenylation signals and polyA tails are well known in the art as important structures for transcription and translation. Capecchi et al do teach that the positive selection marker can in some cases comprise a polyadenylation sequence (see column 13, lines 26-49, in particular). Since Capecchi et al teach a promoterless positive selection marker in a PNS vector and methods to target genes with the vector; it would be obvious to include a polyadenylation signal at the end of each marker gene as taught by Sedivy et al, in order to get proper transcription and translation of the markers. The motivation to combine these elements is the benefit of being able to produce functional selection markers in order to perform the intended gene disrupting method. There is a reasonable expectation of success in creating a PNS vector with a Cre-Lox recombination site for use in gene targeting of somatic cells since this has worked previously in cited references.

Claims 2-4, 6-7, 12, 14-19, 20, 22-25, 28, 31-37, 39-40, 42 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record), in view of Sedivy et al (of record) and further in view of Barsoum (of record). Neither Capecchi et al, Sedivy et al or Barsoum teach a promoter that is a RSV promoter or a PGK promoter. Therefore, the rejection of claims 43-48 and 50 has been withdrawn from this rejection. This rejection of the other claims is being

maintained for reasons of record in the previous Office Action, mailed 4/10/2007 and for reasons outlined below.

Claims 19 and 42 have been newly added to this rejection. Claim 19 is drawn to an *in vitro* method for disrupting a gene of interest in a somatic cell comprising introducing into the cell a targeting vector and a double-stranded oligonucleotide of 62 bp into the cell. Claim 42 is drawn to a somatic cell gene targeting transfection mixture comprising a gene targeting construct and a 62 bp double-stranded oligonucleotide.

Applicants submit that neither Capecchi et al nor Sedivy et al teach a method comprising introducing a double- stranded oligonucleotide into the somatic cell along with the targeting vector. Applicants submit that Barsoum does not remedy the deficiencies of Capecchi et al and Sedivy et al. Barsoum teaches the inclusion of carrier DNA in a transformation mixture. In particular, Barsoum teaches that the carrier DNA is approximately 300 bp to 1000 bp in length (col. 10, lines 52-53). Applicants submit that Barsoum does not teach or suggest the inclusion of a double-stranded oligonucleotide of at least about 20 bp but less than about 200 bp.

Claims 19 and 42 are drawn to the claimed method and mixture with a very specific length for the oligonucleotide of 62 bp. The specification discloses that this oligonucleotide is of random sequence and functions to increase the frequency of homologous recombination. Applicants predicted that the oligonucleotide may serve as a sequence independent decoy for cellular nucleases that would otherwise degrade the targeting vector or that the short oligonucleotide strands would induce DNA repair enzymes that facilitate recombination (see paragraph 0082). Barsoum teaches carrier

DNA that increases the efficiency of transfection. Although Barsoum teaches that the carrier DNA is approximately 300 bp to 1000 bp in length (see column 10, lines 44-50, for example) and not 62 bp in length it would constitute mere routine experimentation to optimize the length of the oligonucleotide from approximately 300 bp to 62 bp. See MPEP 2144.05 (II)(A) Optimization of Ranges:

A.Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Therefore, the combination of Capecchi et al, Sedivy et al and Barsoum render obvious the claimed method and transfection mixture of claims 19 and 42.

Applicant's arguments filed 10/4/2007 have been fully considered but they are not persuasive. The arguments regarding the combination of Capecchi et al and Sedivy et al have been addressed above and are also applicable here. The newly

amended limitation in claims 18 and 32 of "at least about 20 bp but less than about 200 bp" is a relatively broad limitation. Similarly, the newly amended limitation in claims 40 and 51 of "at least about 50 bp but less than about 200 bp" is also a relatively broad limitation. The word "about" has not been given a limiting definition in the specification. Therefore it can be given the broadest reasonable interpretation, for example, about 200 bp can mean 250 bp, 300 bp, 350 bp, etc. and at least about 20 bp or 50 bp can mean 30 bp, 50 bp, 75 bp, 100 bp, 150 bp, 200 bp, etc. for example.

Barsoum teaches that the preferred length of carrier DNA is approximately 300 to 1000 bp in length (col. 10, lines 52-53). The double stranded oligonucleotide can be less than about 200 bp. Using the broadest reasonable interpretation of "about 200 bp", the DNA that is "approximately 300 bp" would meet the limitation of less than about 200 bp. Therefore, the combination of Capecchi et al, Sedivy et al and Barsoum render obvious the claimed method and transfection mixture of claims 2-4, 6-7, 12, 14-19, 20, 22-25, 28, 31-37, 39-42 and 51.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record), in view of Sedivy et al (of record) in view of Pfarr et al (of record) and further in view of Czernilofsky et al (U.S. Patent No. 5,922,549, 7/13/1999). This is a NEW rejection necessitated by amendment to claim 43.

Applicants claim a somatic cell gene targeting vector comprising wherein the expression cassette comprises a BGH polyadenylation sequence. Applicants submit that, independent claim 43 from which claim 49 depends, is very similar to cancelled

claim 1, with the addition of the limitation of the promoter being a RSV promoter or a PGK promoter.

The teachings of Capecchi et al and Sedivy are detailed in the rejection above. Pfarr et al teach a comparison of various polyadenylation regions on gene expression in mammalian cells using a downstream galactokinase marker gene. Pfarr et al teach that a BGH polyA region results in galactokinase expression three times higher than that of SV40 early or human collagen polyA regions (see abstract, in particular).

As detailed in the previous Office Action (mailed 4/10/2007, pages 13-16) the combination of the teaching of Capecchi et al, Sedivy et al and Pfarr et al renders obvious a somatic cell targeting vector comprising a BGH polyadenylation sequence. However, the teaching of Capecchi et al or Sedivy et al or Pfarr et al do not specifically teach a vector with RSV promoter or PGK promoter.

Czernilofsky et al teach a cell comprising a plasmid which can be transfected into mammalian cells and integrated into the host genome, to enable expression of a reporter gene to take place under the control of regulatory elements (see column 7, lines 55-65, for example). Czernilofsky et al teach a RSV LTR promoter as an example of a promoter which drive selection marker genes. Czernilofsky et al teach that the plasmids are preferably designed so that individual important elements such as the reporter gene, and the regulatory sequences for the selection marker can easily be replaced or changed (see column 8, lines 1-25, for example). Therefore, Czernilofsky et al meets the limitation of an RSV promoter operably linked to a selection marker on a plasmid vector.

It would be obvious to modify the targeting vector rendered obvious by Capecchi et al in view of Sedivy et al and further in view of Pfarr et al and use an RSV promoter as taught by Czernilofsky et al in place of the promoters contemplated by Capecchi et al in Table IIB because the claimed promoters were well known in the prior art and the substitution of one known element (i.e. RSV promoter) for another (e.g. CMV promoter) would yield predictable results to the skilled artisan at the time the invention was made. There is a reasonable expectation of success to use RSV promoter in place of a CMV promoter to regulate expression of a negative selection marker because these promoters are known in the art and Czernilofsky et al teach that the RSV promoter can drive expression of a selectable marker. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Capecchi et al (of record) in view of Sedivy et al (of record), in view of Pfarr et al (of record) and further in view of Czernilofsky et al render obvious somatic gene targeting vector comprising a BGH polyadenylation sequence and an RSV promoter **(claim 49)**.

Claims 11 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record), in view of Sedivy et al (of record), in view of Barsoum (of record) and in view of Pfarr et al (of record). This rejection is being maintained for reasons of record in the previous Office Action, mailed 4/10/2007 and for reasons outlined below.

Applicants submit that as discussed above, neither Capecchi et al nor Sedivy et al teach a method comprising introducing a double-stranded oligonucleotide into the somatic cell along with the targeting vector. Applicants submit that Barsoum does not remedy the deficiencies of Capecchi et al. and Sedivy et al. Barsoum teaches the inclusion of carrier DNA in a transformation mixture. In particular, Barsoum teaches that the carrier DNA is approximately 300 to 1000 bp in length (col. 10, lines 52-53). Applicants submit that Barsoum does not teach or suggest the inclusion of a double-stranded oligonucleotide of at least about 20 bp but less than about 200 bp as recited by the pending claims. Applicants submit that Pfarr et al does not remedy the deficiencies of Capecchi et al, Sedivy et al, and Barsoum. Pfarr et al teach a comparison of various polyadenylation regions on gene expression in mammalian cells. Applicants submit that Pfarr et al do not teach or suggest the inclusion of a double-stranded oligonucleotide of at least about 20 bp but less than about 200 bp as recited by the pending claims.

Applicant's arguments filed 10/4/2007 have been fully considered but they are not persuasive. The arguments regarding the combination of Capecchi et al and Sedivy et al have been addressed above and are also applicable here. As discussed above, the newly amended limitation in claims 18 and 32 of "at least about 20 bp but less than about 200 bp" is a relatively broad limitation. The word "about" has not been given a limiting definition in the specification. Therefore it can be given the broadest reasonable interpretation, for example, about 200 bp can mean 250 bp, 300 bp, 350 bp,

etc. and at least about 20 bp can mean 30 bp, 50 bp, 75 bp, 100 bp, 150 bp, 200 bp, etc. for example.

Barsoum teaches that the preferred length of carrier DNA is approximately 300 to 1000 bp in length (col. 10, lines 52-53). The double stranded oligonucleotide can be less than about 200 bp. Using the broadest reasonable interpretation of "about 200 bp", the DNA that is "approximately 300 bp" would meet the limitation of less than about 200 bp. Therefore, the combination of Capecchi et al, Sedivy et al, Barsoum and Pfarr et al render obvious the method of claim 11 and the somatic cell gene targeting transfection mixture of claim 38.

Claims 43 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (of record) in view of Sedivy et al (of record) and further in view of Kucheriapati et al (U.S. Patent No. 6,114,598, 9/5/2000).

It is noted that new claim 53 limits the vector of claim 43 to a vector comprising a promoter that is a phosphoglycerate kinase (PGK) promoter.

The teaching of Capecchi et al and Sedivy et al and the combination of the two have been detailed in the previous Office action (mailed 4/10/2007, pages 5-8, for example). The response to arguments submitted by the Applicants regarding Capecchi et al in view of Sedivy et al is detailed above. Capecchi et al teach a table showing contemplated regulatory sequences (i.e. promoters) for the positive and/or negative selection markers (see column 14, Table IIB, in particular). Capecchi et al or Sedivy et al do not specifically teach a vector with a PGK promoter.

Kucheriapati et al teach a targeting vector for using in mammalian cells to inactivate antibody chains. Kucheriapati et al teach that the targeting vector comprises a PGK promoter operably linked to a negative selection marker that is Diphtheria toxin gene (see column 25, lines 35-50, in particular). Therefore, Kucheriapati et al meets the limitation of a PGK promoter for a negative selection marker on a vector.

It would be obvious to modify the targeting vector rendered obvious by Capecchi et al in view of Sedivy et al and use a PGK promoter as taught by Kucheriapati et al in place of the promoters contemplated by Capecchi et al in Table IIB because the claimed promoters were well known in the prior art and the substitution of one known element (i.e. PGK promoter) for another (e.g. CMV promoter) would yield predictable results to the skilled artisan at the time the invention was made. There is a reasonable expectation of success to use PGK promoter in place of a CMV promoter to regulate expression of a negative selection marker because these promoters are known in the art and Kucheriapati et al teach that the PGK promoter can drive expression of a selectable marker. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Capecchi et al (of record) in view of Sedivy et al (of record) and further in view of Kucheriapati et al render obvious a somatic gene targeting vector comprising an PGK promoter (**claims 43 and 53**).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Laura McGillem Mitchell
Examiner
12/14/2007

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